DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of SEQ ID NO:28 as the species and election of group I invention in the reply filed on 2/22/07 is acknowledged. The traversal arguments were addressed in the office action dated 4/19/07.

The elected species SEQ ID NO: 28 have been found to be free of art. However, upon extending the search, prior art was found on SEQ ID NO: 1.

Claims 1-63 are pending.

Claims 4, 5, 7, 9, 11 and 58 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/22/07.

Claims 412-19 and 26-56 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/22/07.

Claims 59-63 have been added as new claims.

Claims 1-3, 6, 8, 10, 20-25, 57 and 59-63 are examined on the merit.

Any rejections and/or objections made in the previous office action dated 1/9/08 and not specifically mentioned hare are considered as withdrawn.

Maintained Rejections/Objections

Election restrictions

Applicants argue that "The elected species SEQ ID NO: 28 is specifically recited in Claim 11 and encompassed by Claims 4-7 and 9. Accordingly, it is not understood why Claim 11 would not be drawn to the elected species or why Claims 2-3 and not Claims 4-7 and 9".

Applicants arguments have been considered and the reason for withdrawing claims 4, 5, 7, 9 and 11 stems from the 'election of species' practice as illustrated in the MPEP section 803.02 [R-5] for Markush claims. The Markush-type claim be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the nonelected species would be held withdrawn from further consideration. On the other hand, should the examiner determine that the (applicant's) elected species is allowable, the examination of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species (Office's prior art species), the Markush-type claim shall be rejected and claims to the nonelected species (species that does not read on Office's elected species) are held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species (applicant's species)".

In the instant case, the applicant's elected species is SEQ ID NO: 28, comprised of the motif, 'FIVSI' that has been indicated as free of prior art. Search was extended to SEQ ID NO:1.

In accordance with MPEP 803.02, any claim not reading on the prior art found on SEQ ID NO: 1 are thereby withdrawn from further consideration.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 and 21-25 remain rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter as stated in the office action dated 1/9/08 and as reiterated below. Response to applicant's arguments appears at the end of the reiterated rejection. Claim 1 as recited encompasses any and all native polypeptide (protein) of nature. Claims 21-25 as recited encompasses again any and all native proteins and in particular human albumin (claim 23) and transferrin (claims 24 and 25). The polypeptide SEQ ID NO: 589 of WO 01/64834 A2 of Tang, et al., discloses the penta peptide motif FIASA (page 133) as shown below:

VGSQGLVPKKNRPAGKDLGAPSGGPPR KCIP/WQGLLLTAS\LLAL*EAPTTAWL**FI**
ASAPYEVAEGENVHLSVVYLRENLYSY GWYKGKTVEPNQLIAAYVIDTHVRTPGP
AYSGRETISPSGDLHFQNVTLEDTGYYN LQVTYRNSQIEQASHLRVYESVAQPSI
QASSCI.

Key to the above protein sequence:

Amino acid sequence (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine,

R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion.

Response to Arguments

Applicants argue that "SEQ ID NO: 589 of Tang et al. is a predicted amino acid sequence. According to the table on page 121, SEQ ID NO: 589 is predicted from a ' contiga (a set of overlapping DNA sequences obtained by shot-gun DNA sequencing). The predicted amino acid sequence contains FIASA (which is one of the variants encompassed by claim 1). However, FIASA follows shortly after a predicted stop codon, which suggests that it does not form part of a leader sequence for a protein. Accordingly, the Examiner has not shown that Applicant s claimed motif is found naturally in leader sequences for proteins as recited in claim 1. Thus, SEQ ID NO: 589 can not form that basis of a non-statutory subject matter rejection".

Applicant's arguments filed 7/8/08 have been fully considered but they are not persuasive. Because, the instant claims are drawn to a 'polypeptide comprising' i) a leader sequence, the leader sequence comprising a)a secretion pre sequence and b) the motif -X1-X2-X3-X4-X5- and ii) a matured desired protein. The claim as recited reads on any polypeptide sequence that comprises of the motif -X1-X2-X3-X4-X5-. Applicant's argument that the 'FIASA' appears after the stop codon and hence suggests that it does not form a part of the leader sequence for a protein is not convincing. The stop codon is a tri-nucleotide code in the nucleic acid sequence. Also, the fact that peptide sequence of Tang represents a peptide derived from an overlapping DNA sequence obtained by shot-gun DNA sequence from a natural source clearly illustrates that the amino acid sequence for the peptide is derived from a natural source

and hence represents natural product. Since the motif –X1-X2-X3-X4-X5- occurs in a leader sequence, the occurrence of FIASA after the stop codon indicates that it could be the part of the leader sequence of a subsequent protein sequence. Hence the rejection as stated in the office action dated 1/9/08 is proper and maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8, 20-22, 24 and 57 remain rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/64834 A2 of Tang, et al., as stated in the office action dated 1/9/08 and as reiterated below with modifications to reflect amendments to claims. The rejection has been modified to incorporate claim 57. Response to applicant's arguments appears at the end of the rejection.

Applicants claim a polypeptide comprising (i) a leader sequence, the leader sequence comprising (a) a secretion pre sequence, and (b) the following motif: -X1-X2-X3-X4-X5- where XI is phenylalanine, tryptophan, or tyrosine, X2 is isoleucine, leucine, valine, alanine or methionine, X3 is leucine, valine, alanine or methionine, X4 is serine or threonine and X5 is isoleucine, valine, alanine or methionine ; and (ii) a matured desired protein.

The cited reference of Tang, et al., discloses the motif 'FIASA' in SEQ ID NO: 589 (page 133, 3rd sequence in the table) that corresponds to the Seq ID NO: 1 of the instant application as shown in the sequence listing:

```
<210>   1
<211>   5
<212>   PRT
<213>   Artificial Sequence

<220>
<223>   Synthetic polypeptide leader sequence

<220>
<221>   MISC_FEATURE
<222>   1
<223>   CAN BE EITHER Phe OR Trp OR Tyr

<220>
<221>   MISC_FEATURE
<222>   2
<223>   CAN BE EITHER Ile OR Leu OR Val OR Ala OR Met

<220>
<221>   MISC_FEATURE
<222>   3
<223>   CAN BE EITHER Leu OR Val OR Ala OR Met

<220>
<221>   MISC_FEATURE
<222>   4
<223>   CAN BE EITHER Ser OR Thr

<220>
<221>   MISC_FEATURE
<222>   5
<223>   CAN BE EITHER Ile OR Val OR Ala OR Met

<400>   1
Xaa Xaa Xaa Xaa Xaa
1               5
```

The disclosure of the sequence motif FIASA in the cited reference of Tang, et al., meets the limitations of claims 1-3. The instant claims 8, 20-22 and 24 recite a limitation "variant thereof" with reference to albumin secretion pre sequence (claim 8), secretion pre sequence (claim 20), variant or fragment of albumin protein (claim 22) and variant or fragment of transferrin protein (claim 24), since the definition of "variant" has been very broadly as follows: "the term "variant" has been defined very broadly as, "[v]ariant of an albumin pre sequence, as used above, refers to an albumin pre sequence wherein at one or more positions, Other than at those defined by X1, X2, X3, X4 or X5 above, there have been amino acid insertions, deletions, or substitutions, either conservative (as described above) or non-conservative, provided that such

changes still allow the peptide to act as a pre sequence" (bridging paragraph of page 8 and 9 of instant specification). ""[V]ariant", in the context of a desired protein, refers to a protein wherein at one or more positions there have been amino acid insertions, deletions, or substitutions, either conservative or non-conservative, provided that such changes result in a protein whose basic properties, for example enzymatic activity or receptor binding (type of and specific activity), thermo stability, activity in a certain pH-range (pH-stability) have not significantly, been changed. "Significantly" in this context means that one skilled in the art would say that the properties of the variant may still be different but would not be unobvious over the ones of the original protein" (page 19 of instant specification). The definition of the "variant thereof" of the instant specification reads on the protein sequence SEQ ID NO: 589 of the cited reference of Tang, et al. This meets the limitations of claims 20-22 and 24. The claim's language with the transitional phrase 'comprising' allows for an unlimited number of amino acids to be present in a polypeptide, thus in an alternative interpretation, the presence of the motif -X1-X2-X3-X4-X5- in the SEQ ID NO: 589 of the cited reference anticipates limitations of instant claim 57.

Hence, the cited reference of Tang, et al., anticipates the instant invention.

Response to Arguments

Applicants argue that "Claim 1 recites a leader sequence comprising Applicant's claimed motif. Although SEQ ID NO: 589 of Tang et al. discloses the sequence FIASI, there is no disclosure that such a sequence is found in a leader sequence as recited in claim 1. In fact, FIASA follows shortly after a predicted stop codon, which suggests that it does not form part of a leader sequence for a protein. Accordingly, this rejection should be withdrawn".

Applicant's arguments filed 7/8/08 have been fully considered but they are not persuasive. The claim as recited in claim 1 is drawn to a polypeptide comprising a leader sequence, the leader sequence comprising (a) a secretion pre sequence, and (b) the following motif: -X1-X2-X3-X4-X5- and (ii) a matured desired protein. Applicants argument that the 'FIASA' appears after the stop codon and hence suggests that it does not form a part of the leader sequence for a protein is not convincing. The stop codon is a tri-nucleotide code in the nucleic acid sequence. Since the motif -X1-X2-X3-X4-X5- occurs in a peptide sequence after the stop codon; the occurrence of FIASA after the stop codon indicates that it could be the part of the leader sequence of a subsequent protein sequence. Also, the claim's language with the transitional phrase 'comprising' allows for an unlimited number of amino acids to be present in a polypeptide, thus in an alternative interpretation, the presence of the motif -X1-X2-X3-X4-X5- in the SEQ ID NO: 589 of the cited reference anticipates limitations of instant claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 8, 10, 20-25 and 57 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention as stated in the office action dated 4/19/07 as reiterated below. The rejection

has been modified to reflect the change in the claim numbers that is being examined on the merit in this office action and to reflect the amendments made to claims 22 and inclusion of claim 57. Response to applicant's argument appears at the end of the rejection.

Factors to be considered in making the determination as to whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing include:

a. Actual reduction to practice;
b. Disclosure of drawings or structural chemical formulas;
c. Sufficient relevant identifying characteristics such as:
    i. Complete structure,
    ii. Partial structure,
    iii. Physical and/or chemical properties or
    iv. Functional characteristics when coupled with a known or disclosed correlation between function and structure;
d. Method of making the claimed invention;
e. Level of skill and knowledge in the art and
f. Predictability in the art.

While all of these factors are considered, a sufficient number for a *prima facie* case are discussed below.

In the instant application, applicants claim a polypeptide comprising (i) a leader sequence, the leader sequence comprising (a) a secretion pre sequence, and (b) the following motif: -X1-X2-X3-X4-X5- where XI is phenylalanine, tryptophan, or tyrosine, X2 is isoleucine, leucine, valine, alanine or methionine, X3 is leucine, valine, alanine or methionine, X4 is serine or threonine and X5 is isoleucine, valine, alanine or methionine ; and (ii) a mature desired protein.

The claims as recited, encompasses not just the peptide motif defined by $-X_1-X_2-X_3-X_4-X_5-$ but it requires the presence of a leader sequence, a secretion pre sequence and a mature desired protein. The claim does not recite the nature of the 'leader sequence', 'pre sequence' or 'the mature desired protein' in terms of the amino acid sequences that would properly define

each of these different peptides that constitute the claimed polypeptide sequence. The claims do not adequately provide structural characteristics of 'leader sequence', 'the pre sequence' or 'the mature desired protein' that make up the polypeptide that is claimed in the instant invention. The specification does not provide adequate support to the claims as recited in describing the instantly claimed invention wherein individual components (such as leader sequence, pre sequence and mature desired protein) of the claimed polypeptide. Recitation of terms such as 'leader sequence', 'pre sequence' and 'mature desired protein' without properly identifying the structural characteristics of these molecules with required sequence identification numbers (SEQ ID Nos) or structural characteristics lead to lack of written description according to 35 USC 112 first paragraph.

The specification on page 7, lines 3-8 states that, "[A] mature desired protein sequence is the primary amino acid sequence that will be present in the expression product following post-translational processing by the expression system in which the polypeptide of the invention is expressed. The-desired protein is preferably suitable for secretion from a cell in which the polypeptide of the invention is expressed", refers to proteins that are post-translationally modified that are naturally occurring that are secreted from the cells. However, the claim 1 as recited claims a polypeptide comprising of a leader sequence, the leader sequence in turn comprising a secretion pre sequence of motif represented by SEQ ID NO: 1 and a mature desired protein. With the exception of the penta-peptide motif, it is unclear from the claim as recited what is the nature and composition of the leader sequence, the secretion pre sequence and the nature of the mature desired protein in terms of its amino acid sequence that would provide structural aspect to these sequences. In the absence of structural feature that represent the

instantly recited polypeptide the claims encompass any and all known and unknown polypeptides that comprises of the motif represented by SEQ ID NO: 1.

In addition to this claims 8 and 10 recite "albumin secretion pre sequence or a variant thereof". The amended claim 8, further recites that "other than the motif, the variant has at least 9 identical amino acids to the albumin secretion pre-sequence". The term "variant" has been defined very broadly as, "[v]ariant of an albumin pre sequence, as used above, refers to an albumin pre sequence wherein at one or more positions, other than at those defined by X1, X2, X3, X4 or X5 above, there have been amino acid insertions, deletions, or substitutions, either conservative (as described above) or non-conservative, provided that such changes still allow the peptide to act as a pre sequence" (bridging paragraph of page 8 and 9 of instant specification). The claim as recited does not define the size of the leader or the secretion pre-sequence to identify whether the 9 identical amino acid corresponds to a contiguous region or any 9 amino acids in any random order of an albumin secretion pre-sequence. The specification as disclosed does not support the innumerable variations possible commensurate with the scope of the definition provided in the specification. The claims 22 and 24 as recite the limitation "variant thereof" with respect to mature desired protein as "[v]ariant, in the context of a desired protein, refers to a protein wherein at one or more positions there have been amino acid insertions, deletions, or substitutions, either conservative or non-conservative, provided that such changes result in a protein whose basic properties, for example enzymatic activity or receptor binding (type of and specific activity), thermo stability, activity in a certain pH-range (pH-stability) have not significantly, been changed. "Significantly" in this context means that one skilled in the art

would say that the properties of the variant may still be different but would not be unobvious over the ones of the original protein" (page 19 of instant specification).

Thus the broad definition of a variant of an unknown polypeptide wherein the primary structure of the polypeptide itself has not been defined adequately in terms of leader sequence, secretion pre sequence and mature desired protein, a variant of such a polypeptide with a broad definition that provide functional characteristics without structural correlation associated amounts to lack of written description.

According to the specification, only a portion of the cited albumin protein is the polypeptide recited in the instant invention, as the motif as represented by the **penta-peptide** or a **part of the motif** as per claim 20 is not a part of the desired polypeptide. However, the desired polypeptide comprises of the 'leader sequence, 'pre sequence' and 'a mature desired protein'. Therefore, the claims as recited suffer from lack of written description in clearly describing the invention to one skilled in the art. Again, the claims as recited encompass any and all naturally occurring proteins (polypeptides) with no limitations to the size and composition of the peptides with the exception of the presence of a penta-peptide motif. The fact that the claim as recited encompass any and all natural polypeptide combined with lack of description in the specification of the individual components such as 'leader sequence', 'pre sequence' and 'a mature desired protein' that constitute each of the desired polypeptide clearly indicates that to one skilled in the relevant art that the inventor(s), at the time the application was filed, may not have had possession of the claimed invention.

Response to Arguments

1. Applicants argue that "The written description requirement does not require a description of the complete structure of every species within a chemical genus. In Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 1324 (Fed. Cir. 2002), the Federal Circuit made clear that the written description requirement can be satisfied in a number of ways by disclosing, for example, ' complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics See M.P.E.P. § 2163".

Applicant's arguments filed 7/8/08 have been fully considered but they are not persuasive. Although, it is true that complete structure of every species be divulged to satisfy the written description, for a generic claim that encompasses a polypeptide that comprises of leader sequence that comprises secretion pre-sequence and a penta-peptide motif and a mature desired protein, the claim as recited does not provide adequate structural features to provide support for the leader sequence. The penta-peptide motif only provide support for the structural variation within a leader sequence but the description of the leader sequence itself is not adequately supported in the specification to support the claims as recited. The claim also recites a mature protein of limitless possibilities. Moreover, applicants clearly state on page 22 of the reply filed on 7/8/08 that the mature protein as the secreted protein is without its secretion pre or pro sequence. Hence according to the claim as recited with the transition phrase 'comprising', the recited polypeptide allows for an unlimited number of polypeptides (peptide, protein, etc) to be present, in an alternative interpretation.

The term leader sequence itself is well known in the literature as shown by:

Street, 1996, Biochimica et Biophysica Acta, 1305, 87-97. Street discloses the sequences of polynucleotide and peptide in figure 5, on page 92. The disclosed sequence further discloses a species of the instant peptide motif FVLTI (positions 14-18) as a part of the leader sequence.

Munson, 1993, Journal of Bacteriology, 175, 6426-6432, discloses the sequences of polynucleotide and peptide in figure 3, on page 6430. The disclosed sequence further discloses a species of the instant peptide motif FLVSI (positions 11-15) as a part of the leader sequence.

Hence, a clear description of the leader sequence comprising the secretion pre-sequence comprising the instant penta-peptide motif is well documented in the prior art literature.

Therefore, it is all the more reason to provide a clear definition in of the leader sequence to comply with the written description to enable one skilled in the art to recognize that the applicants were in possession of the instant invention.

2. **Claimed Motif**

Applicants argue that "[A]pplicant has provided the complete structure of the crucial element of the claimed invention the -11-12-13-14-15- motif. The -11-12-13-14-15- motif is recited in the application and includes a limited combination of amino acids. The -11-12-13-14-15- motif is defined structurally in Claim 1 as a combination of five amino acids where X1 is phenylalanine, tryptophan, or tyrosine, X2 is isoleucine, leucine, valine, alanine or methionine, X3 is leucine, valine, alanine or methionine, X4 is serine or threonine and X5 is isoleucine, valine, alanine or methionine. Accordingly, the specification adequately describes the claimed motif. To the extent that the Examiner is arguing that Applicants were not in possession of all the

claimed variants, Applicant submits that it was reasonable to predict at the time of filing that all claimed variants would achieve the inventive effect. The data submitted with the attached Declaration of Darrell Sleep shows that claimed variants of FIVSI achieve the same inventive effect as FIVSI itself.

An extensive study was conducted to determine the effect of various conservative substitutions of the FIVSI motif (as defined by Claim 1) at each of its positions. In particular, Applicants tested the ability of the motif within the context of a leader sequence to enhance expression of a recombinant heterologous protein (the protein chosen to illustrate this was recombinant, human albumin; ' rHAa). In addition, the effect of repositioning the motif within the leader sequence has also been tested. The enclosed data demonstrate that claimed variants retain the beneficial effect of the FIVSI motif. Sleep Declaration at ¶ 5.

As supported by the attached data, a motif having one of the defined conservative substitutions at any one of its five positions shares the inventive features of FIVSI, in that it supports an enhanced production of recombinant protein. Given that the conservative substitutions as defined by Claim 1 are acceptable at any position, there is no reason to suspect that a motif having more than one of the conservative substitutions as defined by Claim 1 would not also retain the inventive technical effect of FIVSI. Accordingly, one of skill in the art would consider that Applicant were in possession of the full scope of the motif as claimed.

Furthermore, Figure 2 from the attached declaration shows the precise location of the pentapeptide motif within the pre sequence is not essential for the beneficial effect. Where the FIVSI motif occupies positions ' 17 to ' 21 of the leader sequence as a result of the introduction of an additional isoleucine residue within the leader sequence (i.e. ' FIVSI+Ic0, compared to the '

16 to ' 20 position as exemplified in Figure 1 of the description, high level rHA production is retained. The positioning of the motif at '16 to '20 is indicated in the description at page 19, lines 18-21 to be merely a preferred embodiment for the motif s positioning; there is no suggestion that other positions would be unacceptable.

Moreover, results comparing the rHA production of FIVSI at ' 17 to ' 21 and IIVSI at ' 17 to ' 21, show that the latter motif, which contains a non-conservative substitution at position 1, i.e. a substitution that is outside of the scope of the claims, is less effective at promoting high level rHA production. In fact, not only does the non-conservative substitution result in a motif that is less effective than FIVSI, it also produces a motif that is less effective than the wild-type sequence SFISL. This result shows that the benefit of the present invention cannot be obtained by simply introducing any hydrophobic amino acid in place of one or more of the FIVSI residues; on the contrary the data presented demonstrate that the Applicant has described a limited number of amino acids for use in a motif that provide a clear inventive effect".

Applicant's arguments filed 7/8/08 have been fully considered but they are not persuasive. Because, the claim as recited claims a penta-peptide motif -X1-X2-X3-X4-X5- wherein each of the individual variables X1-X5 are represented by 2 or more different amino acids. The possible number of combinations for this penta-peptide motif is 3x5x4x2x4 = 480. Applicants have shown various conservative substitutions of **one** motif 'FIVSI' in an **albumin secretion pre-sequence** in their study as illustrated in Dr. Sleep's declaration. The claim 1 as recited does identify neither the leader sequence nor the secretion pre-sequence by SEQ ID NO., or by name. Moreover, the variant being defined as "[v]ariant of an albumin pre sequence, as

used above, refers to an albumin pre sequence wherein at one or more positions, other than at those defined by X1, X2, X3, X4 or X5 above, there have been amino acid insertions, deletions, or substitutions, either conservative (as described above) or non-conservative, provided that such changes still allow the peptide to act as a pre sequence" the number of species represented by the instant claims is limitless. Therefore, specification as disclosed is inadequate to support the claim as recited commensurate with the scope of the claims.

3. **Secretion Pre Sequence**

Applicants argue that "[T]he Examiner asserts that ' it is unclear from the claim as recited what is the nature and composition of... the secretions pre sequence.., in terms of its amino acid sequence that would provide structural aspect to these sequences Action at page 6.

First, Applicants note that Claim 11 recites a specific secretion pre sequence in terms of its amino acid sequence. Accordingly, there can be no doubt that Claim 11 satisfies the written description requirements.

Second, Claim 8 was amended to recite ' wherein, other than the motif, the variant has at least 9 identical amino acids to the albumin secretion pre sequence.~ Accordingly, claim 8 and its dependent claims 9 and 10 are directed to an albumin secretion pre sequence or a variant that has at least 9 identical amino acids to the albumin secretion pre sequence. Accordingly, all of the secretion pre sequences share at least 9 of the remaining 13 amino acids of the albumin secretion pre sequence. See Figure 1. In view of this disclosure, those skilled in the art could readily envision all of the species of the claimed genus, and thus, the specification satisfies the written description requirement with respect to at least these Claims 9 and 10. See, e.g., Written

Description Training Materials, March 25, 2008 at Example 10 (claim 2); see also Exparte Bandman, Appeal No. 2004-2319 at p. 5 (BPAI 2005).

Third, those skilled in the art would recognize that the FIVSI motif would have a beneficial effect on protein secretion without limitation to any particular leader sequence or secretion pre sequence. In support, Applicant has submitted the data shown in Figure 3 of the attached declaration. As can be seen from Figure 3, where the invertase leader sequence responsible for secretion of rTF contained FIVSI (i.e. plasmid pDB3606), production of rTF was greater than that from the control yeast strain in which the invertase leader sequence contained the prior art motif SFISL (i.e. plasmid pDB3221). Sleep Declaration at ¶ 15. The data show that the beneficial effect of including FIVSI in a leader sequence is not limited to improving secretion of a desired protein in the context of a modified albumin secretion pre sequence, but extends to improving secretion in the context of other pre sequences, such as a modified invertase pre sequence. Sleep Declaration at ¶ 16. Accordingly, as the identity of the leader sequence and secretion pre sequence is not relevant to the patentability of the pending claims (excluding the FIVSI motif), the written description rejection based on these grounds should be withdrawn".

Applicant's arguments filed 7/8/08 have been fully considered but they are not persuasive.

First, it should be noted that claim 11 has not been rejected under 35 USC 112 (written description).

Secondly, the albumin secretion pre-sequence has not been identified with a SEQ ID NO., and hence, it is difficult to discern the added limitation that 'other than the motif, the variant has at least 9 identical amino acids'. It is not clear which of the 9 amino acids of the remaining 13 residues are identical to the albumin secretion pre-sequence and whether the amino acids that remain identical are contiguous or randomly placed in the albumin secretion pre-sequence.

Applicants state that one skilled in the art would recognize that FIVSI motif would have a beneficial effect on the protein secretion without limitation to any leader or secretion pre-sequence. This is not persuasive given the fact that applicants have shown one example of the motif, namely, FIVSI in an albumin secretion pre-sequence and in the secretion of rTF. As afore-mentioned, the penta-peptides species that reads on the instant penta-peptide motif has been used in the secretion of proteins in the prior art, for example:

Street, 1996, Biochimica et Biophysica Acta, 1305, 87-97. Street discloses the sequences of polynucleotide and peptide in figure 5, on page 92. The disclosed sequence further discloses a species of the instant peptide motif FVLTI (positions 14-18) as a part of the leader sequence.

Munson, 1993, Journal of Bacteriology, 175, 6426-6432, discloses the sequences of polynucleotide and peptide in figure 3, on page 6430. The disclosed sequence further discloses a species of the instant peptide motif FLVSI (positions 11-15) as a part of the leader sequence.

4. **Mature Desired Protein**

Applicants further states that "[T]he Examiner again asserts that ' it is unclear from the claim as recited what is the nature and composition of... the nature of the mature desired protein

in terms of its amino acid sequence that would provide structural aspect to these sequences. Action at page 6.

The term 'mature desired protein' is defined as the secreted protein without its secretion pre sequence or the pre-pro sequence. See page 18, lines 21-25 and page 42, lines 8-11. As with the leader sequence and secretion pre sequence, the identity of the mature desired protein is not relevant to the patentability of the pending claims".

Applicants further state that "It is well established that leader sequences can direct the secretion of desired proteins independently of the identity of the desired protein. Please see Gierasch, 1989, Biochemistry, 28(3), 923-931 (submitted to USPTO in response dated 19 October 2007) which states that' Recombinant proteins composed of a signal sequence from one organism and a mature secretory protein from another organism are frequently export competent (page 923, left column, first paragraph). The fact that they [i.e. signal sequences] can in many instances be transferred from one protein to another and still function implies that they act quite independently of their context (the sequences adjacent). Signal sequences perform their multiple roles while they are attached as N-terminal extensions on their cognate mature proteins; yet they are probably relatively free of interactions with the rest of the nascent chain (page 927, left column, final sentences; emphasis added)".

Applicant's arguments filed 7/8/08 have been fully considered but they are not persuasive.

Applicant's statement that "[T]he term 'mature desired protein' is defined as the secreted protein **without** its secretion pre sequence or the pre-pro sequence", clearly substantiates the lack

of written description of the instant invention. The claim as recited is drawn to "A polypeptide comprising (i) a leader sequence, the leader sequence comprising (a) a secretion pre sequence, **and** (b) the following motif: -X1-X2-X3-X4-X5- **and** (ii) a mature desired protein." The above statement that the mature protein of the claim does not require the presence of the leader sequence comprising the secretion pre-sequence and the penta-peptide motif or vice versa, the claim allows for an unlimited number of peptide, protein, etc., to be present, thus in an alternative interpretation.

With respect arguments on the statements available in Gierasch reference, the arguments made by the applicants have been addressed in our reply dated 1/9/08 on page 9 of the office action as follows: "As seen in the cited reference of Gierasch, it is clearly stated that, the role of signal sequences are still poorly understood (page 923, paragraph 1), the reference further state that "despite this striking conservation of a critical cellular function, signal sequences display a remarkable **lack of primary sequence homology even among closely related proteins**". This clearly illustrates facts that are contrary to applicant's argument that functional definition is sufficient to satisfy the lack of written description in the absence of a structure of the biomolecule to correlate with the function. On page 925, column 2, paragraph 4, Gierasch, further teaches that "**comparison of all known signal sequences reveal no regions of strict homology**". On page 926, column 1, paragraph 1, Gierasch's reference further state that "many reports of alterations in signal sequences, including point mutations that lead to loss of the function". This is contrary to the applicant's argument that, "written description does not require a description of the complete structure of every species within the chemical genus".

Hence, the written description rejection under 35 USC 112, as stated above is proper and maintained.

New ground of rejections

Claim Rejections - 35 USC § 112 (New matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 59-63 recites a limitation "wherein other than the motif, the variant has at least 9 identical amino acids to the (acid phosphatase or invertase, etc.,) protein secretion pre sequence".

There is no literal support or implied support to the afore-mentioned claim limitations in the specification as disclosed or in the submitted sequence listing. The only support of the claims as recited is on page 2 of the specification in lines 5-29 for the various leader sequences of various species disclosed comes from prior art references.

Therefore, the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6, 8, 20-22, 24 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Street, 1996, Biochimica et Biophysica Acta, 1305, 87-97.

Applicants claim a polypeptide comprising (i) a leader sequence, the leader sequence comprising (a) a secretion pre sequence, and (b) the following motif: -X1-X2-X3-X4-X5- where XI is phenylalanine, tryptophan, or tyrosine, X2 is isoleucine, leucine, valine, alanine or methionine, X3 is leucine, valine, alanine or methionine, X4 is serine or threonine and X5 is isoleucine, valine, alanine or methionine ; and (ii) a matured desired protein.

Street discloses the sequences of polynucleotide and peptide in figure 5, on page 92. The disclosed sequence further discloses a species of the instant peptide motif FVLTI (positions 14-18) as a part of the leader sequence that corresponds to Seq ID NO: 1 of the instant application as shown in the sequence listing:

```
<210>  1
<211>  5
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic polypeptide leader sequence

<220>
<221>  MISC_FEATURE
<222>  1
<223>  CAN BE EITHER Phe OR Trp OR Tyr

<220>
<221>  MISC_FEATURE
<222>  2
<223>  CAN BE EITHER Ile OR Leu OR Val OR Ala OR Met

<220>
<221>  MISC_FEATURE
<222>  3
<223>  CAN BE EITHER Leu OR Val OR Ala OR Met

<220>
<221>  MISC_FEATURE
<222>  4
<223>  CAN BE EITHER Ser OR Thr

<220>
<221>  MISC_FEATURE
<222>  5
<223>  CAN BE EITHER Ile OR Val OR Ala OR Met

<400>  1
Xaa Xaa Xaa Xaa Xaa
1               5
```

Hence, reads on the limitations of claims 1 and 6. The instant claims 8, 20-22 and 24 recite a limitation "variant thereof" with reference to albumin secretion pre sequence (claim 8), secretion pre sequence (claim 20), variant or fragment of albumin protein (claim 22) and variant or fragment of transferrin protein (claim 24), since the definition of "variant" has been very broadly as follows: "the term "variant" has been defined very broadly as, "[v]ariant of an albumin pre sequence, as used above, refers to an albumin pre sequence wherein at one or more positions, other than at those defined by X1, X2, X3, X4 or X5 above, there have been amino acid insertions, deletions, or substitutions, either conservative (as described above) or non-conservative, provided that such changes still allow the peptide to act as a pre sequence" (bridging paragraph of page 8 and 9 of instant specification). ""[V]ariant", in the context of a desired protein, refers to a protein wherein at one or more positions there have been amino acid insertions, deletions, or substitutions, either conservative or non-conservative, provided that such changes result in a protein whose basic properties, for example enzymatic activity or receptor binding (type of and specific activity), thermo stability, activity in a certain pH-range (pH-stability) have not significantly, been changed. "Significantly" in this context means that one skilled in the art would say that the properties of the variant may still be different but would not be unobvious over the ones of the original protein" (page 19 of instant specification). The definition of the "variant thereof" of the instant specification reads on the peptide sequence of figure 5 of Street, et al. This meets the limitations of claims 8, 20-22 and 24. The claim's language with the transitional phrase 'comprising' allows for an unlimited number of amino acids to be present in a polypeptide, thus in an alternative interpretation, the presence of the motif -X1-

X2-X3-X4-X5- in the peptide sequence of figure 5 of the cited reference anticipates limitations of instant claim 57.

Hence, the cited reference of Street, et al., anticipates the instant invention.

Claims 1, 2, 4, 6, 8, 20-22, 24 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Munson, 1993, Journal of Bacteriology, 175, 6426-6432.

Munson, 1993, Journal of Bacteriology, 175, 6426-6432, discloses the sequences of polynucleotide and peptide in figure 3, on page 6430. The disclosed sequence further discloses a species of the instant peptide motif FLVSI (positions 11-15) as a part of the leader sequence that corresponds to Seq ID NO: 1 as shown above. Hence reads on the limitations of claims 1, 2, 4 and 6. The instant claims 8, 20-22 and 24 recite a limitation "variant thereof" with reference to albumin secretion pre sequence (claim 8), secretion pre sequence (claim 20), variant or fragment of albumin protein (claim 22) and variant or fragment of transferrin protein (claim 24), since the definition of "variant" has been very broadly as follows: "the term "variant" has been defined very broadly as, "[v]ariant of an albumin pre sequence, as used above, refers to an albumin pre sequence wherein at one or more positions, other than at those defined by X1, X2, X3, X4 or X5 above, there have been amino acid insertions, deletions, or substitutions, either conservative (as described above) or non-conservative, provided that such changes still allow the peptide to act as a pre sequence" (bridging paragraph of page 8 and 9 of instant specification). ""[V]ariant", in the context of a desired protein, refers to a protein wherein at one or more positions there have been amino acid insertions, deletions, or substitutions, either conservative or non-conservative, provided that such changes result in a protein whose basic properties, for example enzymatic

activity or receptor binding (type of and specific activity), thermo stability, activity in a certain pH-range (pH-stability) have not significantly, been changed. "Significantly" in this context means that one skilled in the art would say that the properties of the variant may still be different but would not be unobvious over the ones of the original protein" (page 19 of instant specification). The definition of the "variant thereof" of the instant specification reads on the peptide in figure 3, on page 6430 of Munson, et al. This meets the limitations of claims 8, 20-22 and 24. The claim's language with the transitional phrase 'comprising' allows for an unlimited number of amino acids to be present in a polypeptide, thus in an alternative interpretation, the presence of the motif -X1-X2-X3-X4-X5- in the peptide sequence of peptide in figure 3, on page 6430 of the cited reference anticipates limitations of instant claim 57.

Hence, the cited reference of Munson, et al., anticipates the instant invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
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